

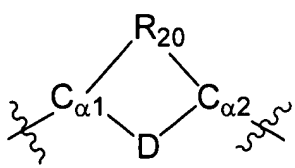
### REMARKS

By this Amendment, claims 8-9, 14-20 and 23-24 are amended. Claims 8-26 are currently pending. Support for the amendments to the specification and claims can be found in the originally filed specification and claims. No new matter has been added.

Specifically, support for the Amendment to claim 9 can be found in the discussion of the “use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for ... influencing blood coagulation, *inflammatory response*, or fibrinolysis ...” in the written description found in the Original Application at page 27, lines 12-15, (*emphasis added*) and the originally filed claims.

Further, support for the Amendment replacing Formula (III) and its corresponding substructure of Formula (I) with a revised depiction of the ring structure can be found in the original circular structure as drawn and the written description found, *inter alia*, in the Original Application at page 2, line 33, through page 3, line 1, and page 3, line 30 through page 4, line 12, and the originally filed claims.

Additionally, support for the Amendment to Formula (I) and replacement of

Formula (III) with the ring structure  is inherent in the definitions of Formulae (I) and (III) in the originally filed application.

Specifically, C<sub>α1</sub> and C<sub>α2</sub> represent the carbons adjacent to D in the ring structure of Formula (I) and its substructure Formula (III) found in the Original Application, page 1, line 6, and page 4, lines 1-12. The carbons are labeled with subscripts to more

clearly define the invention. Specifically,  $C_{\alpha 1}$  and  $C_{\alpha 2}$  are independently defined as -CH- and -C- in the currently amended claims to more clearly define the ring structure.

The remainder of the ten-sided ring in Formulae (I) and (III) in the Original Application has also been replaced by  $R_{20}$  to more clearly define the invention. Support for  $R_{20}$  is inherent in the definitions of Formula (III) and the corresponding substructure of Formula (I) in the Original Application. The ten-sided ring was defined as “a mono- or bicyclic 5- to 10-membered carbocyclic aryl group,” “phenyl,” “a mono- or bicyclic 5-to 10-membered heterocyclic group (Het),” and “pyridyl.” (Original Application, page 4, lines 1-12.) To define the ring as an unsubstituted or substituted phenyl and an unsubstituted or substituted pyridyl (see the Original Application at page 4, lines 5-6 and lines 11-12, respectively) in currently amended claim 14,  $R_{20}$  is defined as an unsubstituted or substituted  $C_3$  alkyl wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen, an unsubstituted or substituted  $C_3$  alkenyl, and an unsubstituted or substituted  $C_3$  alkenyl wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen. Thus,  $R_{20}$ , together with  $C_{\alpha 1}$ ,  $C_{\alpha 2}$ , and D, more explicitly recite the antecedent terms phenyl and pyridyl.

To define the ring as an unsubstituted or substituted 6-membered carbocyclic aryl group and an unsubstituted or substituted 6-membered heterocyclic group (see the Original Application at page 4, lines 2-12),  $R_{20}$  is defined as an unsubstituted or substituted  $C_3$  alkyl wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen, an unsubstituted or substituted  $C_3$  alkenyl, and an unsubstituted or substituted  $C_3$  alkenyl wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen.

Thus,  $R_{20}$ , together with  $C_{\alpha 1}$ ,  $C_{\alpha 2}$ , and D, more explicitly recite the antecedent terms 6-membered carbocyclic aryl group and 6-membered heterocyclic group.

To define the ring as unsubstituted or substituted bicyclic 7- or 10-membered carbocyclic aryl group and an unsubstituted or substituted bicyclic 7- to 10-membered heterocyclic group (see the Original Application at page 4, lines 2-4 and lines 7-10, respectively),  $R_{20}$  is defined as an unsubstituted or substituted  $C_4$ - $C_7$  alkyl comprising a ring wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen, an unsubstituted or substituted  $C_4$ - $C_7$  alkenyl comprising a ring, and an unsubstituted or substituted  $C_4$ - $C_7$  alkenyl comprising a ring wherein at least one carbon is replaced with nitrogen, sulfur, or oxygen. Thus,  $R_{20}$ , together with  $C_{\alpha 1}$ ,  $C_{\alpha 2}$ , and D, more explicitly recite the antecedent terms bicyclic 7- or 10-membered carbocyclic aryl group and bicyclic 7- to 10-membered heterocyclic group.

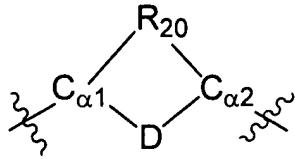
Further support for the Amendments can be found in the definitions of these groups in the Original Application at page 14, lines 13-26, 28-32, page 15, line 29 through page 16, line 20, and page 17, line 20, through page 20, line 28, and the originally filed claims.

**REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

**A. The Examiner Rejects Claims 8-26 Under 35 U.S.C. § 112, First Paragraph**

The Examiner rejects claim 8-26 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement." (Office Action at 2). The Examiner argues that "[t]he claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." (*Id.* at 2-3). The Examiner also rejects the claims because the substructure of Formula I (i.e., Formula III) "is confusing as to what the structure is." (*Id.* at 2). Specifically, the Examiner states that it "lacks antecedent basis in the description as originally filed." (*Id.* at 2).

In an effort to clarify the ring structure, Applicants have amended the specification and amended claims 14-20 and 23-24. Specifically, Applicants amended the formulae in the specification and claims to clarify that the ring structure B, together with D and the two carbon atoms to which D is attached, can be a 6- to a 10-membered

ring. In particular, Applicants have replaced Formula III with  ("the ring structure") and revised the corresponding section in Formula I, so that the ring structure can be of various carbon or heteroatoms as originally defined in the ten-sided ring of the claimed invention.

As Applicants had elected phenyl, optionally substituted with R<sup>1</sup>, in light of the restriction requirement made by the Examiner in the February 3, 2003, Office Action, Applicants currently amended claim 14 to include phenyl and pyridyl moieties in the ring of Formula (I). By defining the variable R<sub>20</sub> as 3 atoms in length in claim 14 to complete the ring structure, Applicants believe that one of ordinary skill in the art reading the claimed possible choices for the ring substructure would be readily able to draw several 6-membered ring structures that fit within the definitions provided for Formula III in the original application. Applicants submit that one of skill in the art would know that the phenyl and pyridyl moieties share electronic and structural properties and are therefore isosteres. Further, they are sufficiently similar to warrant inclusion as alternatives in Formula (I) and therefore alternatives within a single claim. Applicants thank the Examiner for her willingness to examine the phenyl and pyridyl, together, as claimed in currently amended claim 14.

For the reasons presented above, Applicants respectfully submit that amended Formula I and the ring structure replacing Formula III more clearly point out the claimed invention. In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8-26 under 35 U.S.C. § 112, First Paragraph.

**B. The Examiner Rejects Claims 9-11 and 21-26  
Under 35 U.S.C. § 112, First Paragraph**

The Examiner rejects claims 9-11 and 21-26 under 35 U.S.C. § 112, first paragraph, as "lacking descriptive support for the claimed scope." (Office Action at 4).

The Examiner argues that “[t]he broad scope encompassing ‘any and all’ prodrug for which descriptive and enabling support have not been found in the specification is still in claim 9 or its dependent claims.” (*Id.* at 4).

Applicants respectfully submit that claims 10 and 21-23 are not dependent on claim 9 and therefore request that the § 112 rejection be withdrawn as to those claims.

Applicants respectfully traverse the Examiner’s argument regarding claim 9 and its dependent claims 11 and 24-26. Applicants submit that claim 9 does not encompass an anticoagulant that can “treat all cardiovascular disorders” as stated by the Examiner. (*Id.* at 4.) The amended claim encompasses pharmaceutical compositions, including prodrugs, for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response, or fibrinolysis, not all cardiovascular disorders. Antecedent support for amended claim 9 can be found in the written description of the Original Application at page 27, lines 14-15, and the originally filed claims, as discussed above. Applicants therefore argue that the rejection is improper.

In view of the foregoing amendments and corresponding arguments, reconsideration and withdrawal of this rejection are respectfully requested.

**REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

The Examiner rejects claim 14 under 35 U.S.C. § 112, second paragraph. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” (Office Action at 3.)

The Examiner indicated that the “notation of ‘B’ is confusing.” (*Id.* at 3.) Claim 14 has been amended to eliminate the ring element “B” from the structural depictions of the compounds of claim 14. Specifically, the “B” notation of the ring has been replaced with R<sub>20</sub>. By defining the variable R<sub>20</sub> in claim 14 as 3 atoms in length to complete the ring structure and defining the ring structure as phenyl and pyridyl, Applicants believe that one of ordinary skill in the art reading the amended claim would be readily able to draw the 6-membered ring structures that fit within the definitions provided for Formula III in the original application. Applicants submit that this Amendment more particularly points out and distinctly claims the ten-sided compounds of Formula I originally recited in the application.

In view of the foregoing amendments, reconsideration and withdrawal of this section 112, second paragraph, rejection are respectfully requested.

**REJECTION UNDER 35 U.S.C. § 132**

The Examiner rejects the Amendment to the specification under 35 U.S.C. § 132. The Examiner argues that the Amendment made in Paper No. 11 “introduces new matter into the disclosure.” (*Id.* at 3). The ring structure submitted in Paper No. 11 has been cancelled from the claims and specification and this rejection is moot.

**REJECTIONS UNDER 35 U.S.C. § 103**

**1. Beight in view of Klein**

The Examiner rejects claims 8-26 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,417,200 to Beight *et al.* ("Beight") in view of U.S. Patent Application Publication No. 2002/0016339 to Klein *et al.* ("Klein") or, alternatively, over Klein in view of Beight. Applicants respectfully traverse the rejection.

According to M.P.E.P. § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met, including that there must be some suggestion or motivation to modify the reference or to combine reference teachings. Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. § 2143 (8<sup>th</sup> Ed. 2001). Further, the evidence of a teaching, suggestion, or motivation to combine the references must be "clear and particular." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see *ex parte Clapp*, 227 U.S.P.Q. 972 (Pat. App. 1985). Applicants respectfully submit the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a) for the reasons set forth below.

The Examiner rejects claims 8-26 under 35 U.S.C. § 103(a) over Beight in view of Klein "for reason[s] of record." (Office Action at 3.) The Examiner argues that Beight teaches "the limitation of Q and Q' being bond or oxygen and X being C<sub>1-6</sub> alkylene" and that Beight specifically teaches "one of Q or Q' is 'O', the other is bond and X is methylene structure" at col. 45-46, examples 32-33. (*Id.* at 3.) Applicants respectfully argue that Beight does not teach or suggest all the claim elements.



Beight does not teach or suggest a compound of Formula (I). Beight teaches a phenyl ring but it is limited to the isomer with substituents in the ortho positions. Beight does not teach or suggest a compound of Formula (I) wherein the ring structure is phenyl and wherein the linker groups are substituted in the meta positions. Further, Beight does not teach or suggest a compound of Formula (I) wherein the ring structure is pyridyl and wherein the linker groups are substituted on the pyridyl ring in the meta positions. The claimed position isomers are not barred from patentability based on structural similarities with the prior art. See, e.g., *In re Papesch*, 315 F.2d 381, 387, 137 U.S.P.Q. 43, 48 (C.C.P.A. 1963) (Holding homologs, isomers and analogs patentable over the prior art) citing *In re Schechter*, 205 F.2d 185, 98 U.S.P.Q. 144 (C.C.P.A. 1953); *Ex parte Hogg*, 121 U.S.P.Q. 96, 98 (Bd. Pat. App. 1958) (stating "isomerism alone cannot negative patentability of one compound over another, since obviously the isomers must be of such relationship structurally that one would be suggestive of the other."); *Schechter*, 205 F.2d at 190, 98 U.S.P.Q. at 150 ("This court has ... implicitly indicated ... that homologs and isomers may be patentable if they are inventive over known prior art compounds.").

In fact, isomerism alone should not raise a *prima facie* case of obviousness. See, e.g., *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 870, 871-72 (Fed. Cir. 1985); *Ex part Mowry*, 91 U.S.P.Q. 219, 221 (Bd. Pat. App. 1950) (rejecting the proposition that isomers, in a broad sense, are necessarily equivalent). Further, the Federal Circuit has reasoned that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *Grabiak*, 769 F.2d at 731, 226

U.S.P.Q. at 872. Thus, Applicants argue that the teaching of the phenyl ring in Beight does not render the present invention obvious.

Additionally, the compounds of the present invention differ from the prior art in the substituents attached to the ring structure. Specifically, Beight does not teach or suggest a compound of Formula (I), wherein  $R_0$  is chosen from a phenyl, wherein the phenyl is mono-, di- or trisubstituted independently of one another by  $R^2$ , and a mono- or bicyclic 5- to 10-membered heteroaryl, as presently claimed. Beight also does not teach or suggest a compound of Formula (I) wherein the nitrogen adjacent to V is singly bonded to a carbon atom, wherein the carbon atom is singly bonded to a substituent A and a substituent L. Specifically, Beight does not teach or suggest a compound of Formula (I) wherein the substituent L is chosen from a direct bond and an unsubstituted or substituted ( $C_1$ - $C_3$ )-alkylene, as presently claimed.

While the Examiner points out that Beight teaches the limitation of Q and Q' are a bond or oxygen and that X can be  $C_1$  alkylene, and that examples 32-33 at col. 45-46 of Beight teach "one of Q or Q' is 'O', the other is bond and X is [a] methylene structure," Beight does not teach or suggest a compound of Formula (I). Applicants argue that the rejection based on the limitations of Q, Q', and X, alone and without reference to the entirety of Formula (I), is improper. In determining obviousness, the subject matter of the claimed invention and the prior art must be considered "as a whole." 35 U.S.C. §103(a); See, e.g., *In re Lancer*, 465 F.2d 896, 898, 175 U.S.P.Q. 169, 171 (C.C.P.A. 1972) (Holding "elementary ... the concept of having to show obviousness of the invention 'as a whole,' as required by 35 USC 103"); *In re Mehta*, 347 F.2d 859, 146 U.S.P.Q. 284, 287 (C.C.P.A. 1965) ("A compound is not ... merely a structural formula;

its properties as part of the whole must be considered”) citing *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43. Specifically, consideration of R<sub>0</sub>, V, A, L, and Formula (I) in its entirety precludes a finding of obviousness based on the isomeric properties of the ring structure.

Applicants further submit that Klein does not overcome the deficiencies of Beight. The Examiner relies on Klein for teaching the “insertion of one methylene between the amido linker and the aminoimino substituted phenyl.” (Office Action at 3.) Applicants have examined the reference and cannot find an aminoimino substituted phenyl in Klein. Applicants have also examined the previous Office Action, Paper No. 9, for guidance and remain unsuccessful at finding an aminoimino substituted phenyl. Therefore, Applicants respectfully request that the rejection be further explained or withdrawn.

## **2. Klein in view of Beight**

The Examiner rejects claims 8-26 under 35 U.S.C. § 103(a) over U.S. Patent Application Publication No. 2002/0016339 to Klein in view of U.S. Patent No. 6,417,200 to Beight. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. M.P.E.P. § 2143 (8<sup>th</sup> ed. 2001); *see also supra*. Specifically, Applicants respectfully submit that the Examiner has failed to establish that the prior art references, alone or combined, teach or suggest all the claim elements.

Applicants submit that Klein does not teach a compound of Formula (I) wherein the ring structure is defined as in the present invention. Klein teaches a phenyl ring wherein the positions of a substituent (e.g., aryl or heteroaryl) and the linker are limited

to the 4-, or para, position on the phenyl ring. (See, e.g., pages 10-16 and 37-43 in Klein). Klein does not teach or suggest a compound of Formula (I) wherein the ring structure is phenyl and wherein the linker groups are substituted on the phenyl ring in the meta positions. Applicants argue that the teaching of the phenyl ring in Klein does not render the present invention obvious because of the differences and reasons discussed above with respect to the phenyl ring in Beight. *See supra*. Further, Klein does not teach or suggest a compound of Formula (I) wherein the ring structure is pyridyl. Specifically, Klein also does not teach or suggest a compound of Formula (I) wherein the linker groups are substituted on the pyridyl ring in the meta positions.

Klein does not teach or suggest a compound of Formula (I), wherein  $R_0$  is chosen from a phenyl, wherein the phenyl is mono-, di- or trisubstituted independently of one another by  $R^2$ , and a mono- or bicyclic 5- to 10-membered heteroaryl, as presently claimed. Klein also does not teach or suggest a compound of the Formula (I) wherein X is a  $(C_1-C_6)$ -alkylene, as presently claimed. Additionally, Klein does not teach or suggest a compound of the Formula (I) wherein Q and Q' are different and are chosen from a direct bond and -O-, as presently claimed. Moreover, Klein does not teach or suggest a compound of the Formula (I) wherein X is a  $(C_1-C_6)$ -alkylene, as presently claimed.

Additionally, Klein does not teach or suggest a compound of Formula (I) wherein the nitrogen adjacent to V is singly bonded to a carbon atom, wherein the carbon atom is singly bonded to a substituent A and a substituent L. Specifically, Klein does not teach or suggest a compound of Formula (I) wherein the substituent L is chosen from a direct bond and an unsubstituted or substituted  $(C_1-C_3)$ -alkylene, as presently claimed.

Applicants submit, that because the subject matter of the claimed invention and the prior art must be considered "as a whole," the rejection based on 35 U.S.C. § 103(a) over Klein in view of Beight should be withdrawn. 35 U.S.C. §103(a); *See also supra*.

Applicants further submit that Beight does not overcome the deficiencies of Klein. Specifically, the combination does not teach or suggest a compound of Formula (I) wherein the ring structure is phenyl or pyridyl and wherein the linker groups are substituted in the meta positions. Additionally, the combination does not teach or suggest a compound of Formula (I), wherein  $R_0$  is chosen from a phenyl, wherein the phenyl is mono-, di- or trisubstituted independently of one another by  $R^2$ , and a mono- or bicyclic 5- to 10-membered heteroaryl, as presently claimed. The combination also does not teach or suggest a compound of Formula (I) wherein the nitrogen adjacent to V is singly bonded to a carbon atom, wherein the carbon atom is singly bonded to a substituent A and a substituent L. The combination does not teach or suggest a compound of Formula (I) wherein the substituent L is chosen from a direct bond and an unsubstituted or substituted ( $C_1$ - $C_3$ )-alkylene, as presently claimed.

Applicants respectfully submit that the combination of references fails to teach or suggest all the claim elements. Neither Klein in view of Beight, nor Beight in view of Klein, teach or suggest a compound of Formula (I) considered in its entirety. Specifically, neither reference, nor their combination, teaches or suggests a compound of Formula (I) wherein the ring structure and its substituents are defined as in the present invention. Further, neither reference, nor their combination, teaches or suggests a compound of Formula (I) wherein the ring structure is phenyl or pyridyl, wherein the linker groups are substituted on the phenyl or pyridyl ring in the meta

positions, and wherein  $R_0$ ,  $Q$ ,  $X$ ,  $Q'$ ,  $D$ ,  $R_{10}$ ,  $R_{20}$ ,  $C_{\alpha 1}$ ,  $C_{\alpha 2}$ , and  $V$  of Formula (I) are as presently defined.

Applicants respectfully submit that, for the reasons discussed above, the combination of references fails to teach or suggest all the claim elements.

These Amendments under 37 C.F.R. § 1.116 should allow for immediate action by the Examiner. The proposed Amendments, moreover, place the claims in condition for allowance or, at least, in better form for appeal, if necessary.

### **CONCLUSION**

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

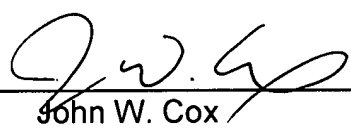
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: April 9, 2004

By: \_\_\_\_\_

  
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